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NEWS 2	Apr 08	"Ask CAS" for self-help around the clock
NEWS 3	Jun 03	New e-mail delivery for search results now available
NEWS 4	Aug 08	PHAPMAMarketLetter(PHARMAML) - new on STN
NEWS 5	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 6	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 7	Sep 03	JAPIO has been reloaded and enhanced
NEWS 8	Sep 16	Experimental properties added to the REGISTRY file
NEWS 9	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 10	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 11	Oct 24	BEILSTEIN adds new search fields
NEWS 12	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 13	Nov 18	DKILIT has been renamed APOLLIT
NEWS 14	Nov 25	More calculated properties added to REGISTRY
NEWS 15	Dec 04	CSA files on STN
NEWS 16	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 17	Dec 17	TOXCENTER enhanced with additional content
NEWS 18	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS 19	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS 20	Feb 13	CANCERLIT is no longer being updated
NEWS 21	Feb 24	METADEX enhancements
NEWS 22	Feb 24	PCTGEN now available on STN
NEWS 23	Feb 24	TEMA now available on STN
NEWS 24	Feb 26	NTIS now allows simultaneous left and right truncation
NEWS 25	Feb 26	PCTFULL now contains images
NEWS 26	Mar 04	SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 27	Mar 19	APOLLIT offering free connect time in April 2003
NEWS 28	Mar 20	EVENTLINE will be removed from STN
NEWS 29	Mar 24	PATDPAFULL now available on STN
NEWS 30	Mar 24	Additional information for trade-named substances without structures available in REGISTRY
NEWS 31	Apr 11	Display formats in DGENE enhanced
NEWS 32	Apr 14	MEDLINE Reload
NEWS 33	Apr 17	Polymer searching in REGISTRY enhanced
NEWS 34	Apr 21	Indexing from 1947 to 1956 being added to records in CA/CAPLUS
NEWS 35	Apr 21	New current-awareness alert (SDI) frequency in WPIDS/WPINDEX/WPIX

NEWS EXPRESS April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP), AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003

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 NEWS HOURS     STN Operating Hours Plus Help Desk Availability
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FILE 'HOME' ENTERED AT 16:36:11 ON 24 APR 2003

=> fil reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

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STRUCTURE FILE UPDATES:   23 APR 2003  HIGHEST RN 504385-01-7
DICTIONARY FILE UPDATES:  23 APR 2003  HIGHEST RN 504385-01-7

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

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Experimental and calculated property data are now available.  See HELP
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in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
Uploading 09913373.str

L1      STRUCTURE UPLOADED

=> d
L1 HAS NO ANSWERS
L1              STR
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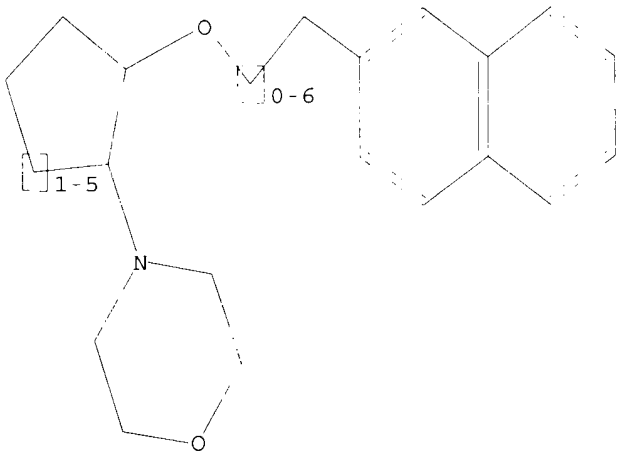

Structure attributes must be viewed using STN Express query preparation.

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=> s l1 sss sam
SAMPLE SEARCH INITIATED 16:36:53 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -     23 TO ITERATE

100.0% PROCESSED      23 ITERATIONS                                1 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          173 TO      747
PROJECTED ANSWERS:               1 TO       80

L2             1 SEA SSS SAM L1

=> s l1 full
FULL SEARCH INITIATED 16:36:57 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    528 TO ITERATE

100.0% PROCESSED     528 ITERATIONS                               8 ANSWERS
SEARCH TIME: 00.00.01

L3             8 SEA SSS FUL L1

=> fil caplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                              148.15     148.36

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FILE COVERS 1907 - 24 Apr 2003 VOL 138 ISS 17
FILE LAST UPDATED: 23 Apr 2003 (20030423/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l3 full
L4 5 L3

=> d l4 1-5 ibib abs histr
'HISTR' IS NOT A VALID FORMAT FOR FILE 'CAPLUS'

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ABS --------- GI and AB
ALL --------- BIB, AB, IND, RE
APPS -------- AI, PRAI
BIB --------- AN, plus Bibliographic Data and PI table (default)
CAN --------- List of CA abstract numbers without answer numbers
CBIB -------- AN, plus Compressed Bibliographic Data
DALL -------- ALL, delimited (end of each field identified)
DMAX -------- MAX, delimited for post-processing
FAM --------- AN, PI and PRAI in table, plus Patent Family data
FBIB -------- AN, BIB, plus Patent FAM
IND --------- Indexing data
IPC --------- International Patent Classifications
MAX --------- ALL, plus Patent FAM, RE
PATS -------- PI, SO
SAM --------- CC, SX, TI, ST, IT
SCAN -------- CC, SX, TI, ST, IT (random display, no answer numbers; SCAN must be entered on the same line as the DISPLAY, e.g., D SCAN or DISPLAY SCAN)
STD --------- BIB, IPC, and NCL

IABS -------- ABS, indented with text labels
IALL -------- ALL, indented with text labels
IBIB -------- BIB, indented with text labels
IMAX -------- MAX, indented with text labels
ISTD -------- STD, indented with text labels

OBIB -------- AN, plus Bibliographic Data (original)
OIBIB ------- OBIB, indented with text labels

SBIB -------- BIB, no citations
SIBIB ------- IBIB, no citations

HIT --------- Fields containing hit terms
HITIND ------ IC, ICA, ICI, NCL, CC and index field (ST and IT) containing hit terms
HITRN ------- HIT RN and its text modification
HITSTR ------ HIT RN, its text modification, its CA index name, and

its structure diagram
HITSEQ ------ HIT RN, its text modification, its CA index name, its structure diagram, plus NTE and SEQ fields
FHITSTR ----- First HIT RN, its text modification, its CA index name, and its structure diagram
FHITSEQ ----- First HIT RN, its text modification, its CA index name, its structure diagram, plus NTE and SEQ fields
KWIC -------- Hit term plus 20 words on either side
OCC --------- Number of occurrence of hit term and field in which it occurs

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ENTER DISPLAY FORMAT (BIB):all

L4 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2003 ACS
AN 2001:591832 CAPLUS
DN 136:63572
TI pH-dependent blocking actions of three novel antiarrhythmic compounds on K+ and Na+ currents in rat ventricular myocytes
AU Franciosi, S.; McLarnon, J. G.
CS Department of Pharmacology and Therapeutics, University of British Columbia, Faculty of Medicine, Vancouver, BC, V6T 1Z3, Can.
SO European Journal of Pharmacology (2001), 425(2), 95-107
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier Science B.V.
DT Journal
LA English
CC 1-3 (Pharmacology)
AB Three novel chem. related compds. were studied for their pH-dependent ion channel blocking actions on the transient outward K+ current (Ito) and the Na+ current (INa) in isolated rat ventricular myocytes. The (.+-.)-trans-naphthylethoxycyclohexylamines, RSD1108, RSD1070 and RSD1067, showed similar potencies in reducing the inactivation time course of Ito at pH 7.4. However, RSD1108 (pKa 6.8) was a more potent blocker of Ito at pH 6.4 than the other two compds. (pKa values near 8.0). The redn. of inactivation times induced by the RSD compds. was consistent with open channel blockade and in consequence an open channel block model was used in order to est. blocking and unblocking rate consts. This anal. showed no apparent correlation between pKa and onward blocking rate consts. for the compds. However, the unblocking rate const. for the low pKa compd. RSD1108 at acid pH decreased markedly from that found at normal pH. Both RSD1108 and RSD1070 showed an enhanced potency to block INa at acid pH relative to pH 7.4. However, RSD1108 showed significantly less inhibition of INa at both pH values compared to RSD1070 and RSD1067. Differences in channel block were also evident between RSD1070 and RSD1067, which could be attributed to the difference in naphthyl groups between their chem. structures. The compds. exhibited use- and frequency-dependent blockade of INa with the amt. of use-dependent blockade greater for RSD1108 and RSD1067 than for RSD1070 at acid pH compared to neutral pH. Greater frequency-dependent inhibition was apparent for RSD1108 as compared to RSD1070 and RSD1067 at both pH 7.4 and 6.4. These results point out the

importance of the magnitude of pKa and chem. structure in ion channel blocking actions of a series of structurally related compds.

ST naphthylethoxycyclohexylamine structure antiarrhythmic pH ion channel blocker

IT Heart, disease
(ischemia; pH-dependent blocking actions of novel antiarrhythmic compds. on K+ and Na+ currents in rat ventricular myocytes)

IT Antiarrhythmics
(pH-dependent blocking actions of novel antiarrhythmic compds. on K+ and Na+ currents in rat ventricular myocytes)

IT Structure-activity relationship
(potassium channel-blocking; pH-dependent blocking actions of novel antiarrhythmic compds. on K+ and Na+ currents in rat ventricular myocytes)

IT Ion channel blockers
(potassium; pH-dependent blocking actions of novel antiarrhythmic compds. on K+ and Na+ currents in rat ventricular myocytes)

IT Structure-activity relationship
(sodium channel-blocking; pH-dependent blocking actions of novel antiarrhythmic compds. on K+ and Na+ currents in rat ventricular myocytes)

IT Ion channel blockers
(sodium; pH-dependent blocking actions of novel antiarrhythmic compds. on K+ and Na+ currents in rat ventricular myocytes)

IT Heart
(ventricle, myocyte; pH-dependent blocking actions of novel antiarrhythmic compds. on K+ and Na+ currents in rat ventricular myocytes)

IT 12408-02-5, Hydrogen ion, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gradient; pH-dependent blocking actions of novel antiarrhythmic compds. on K+ and Na+ currents in rat ventricular myocytes)

IT **244762-60-5**, RSD 1067 244762-62-7, RSD1070 244762-87-6, RSD 1108
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)
(pH-dependent blocking actions of novel antiarrhythmic compds. on K+ and Na+ currents in rat ventricular myocytes)

IT 17341-25-2, Sodium ion, biological studies 24203-36-9, Potassium ion, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pH-dependent blocking actions of novel antiarrhythmic compds. on K+ and Na+ currents in rat ventricular myocytes)

RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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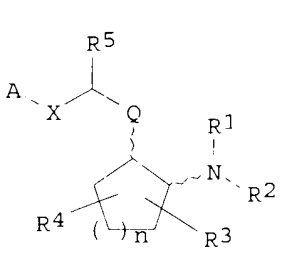
(26) Yong, S; J Pharmacol Exp Ther 1999, V289, P236 CAPLUS

L4 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2003 ACS
AN 2000:573767 CAPLUS
DN 133:176973
TI Cycloalkyl amine compounds and their use as antiarrhythmics and sodium channel blockers
IN Beatch, Gregory N.; Plouvier, Bertrand M. C.; Walker, Michael J. A.; Wall, Richard A.; Zolotoy, Alexander B.
PA Nortran Pharmaceuticals Inc., Can.
SO PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C217-00
CC 24-4 (Alicyclic Compounds)
Section cross-reference(s): 1, 27, 28
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000047547	A2	20000817	WO 2000-CA117	20000210
WO 2000047547	A3	20001214		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-119887P P 19990212
OS MARPAT 133:176973
GI



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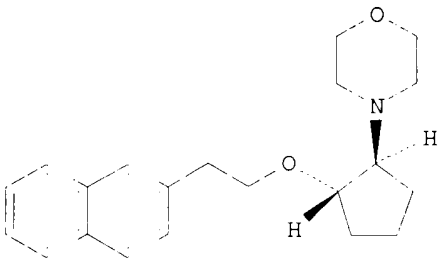

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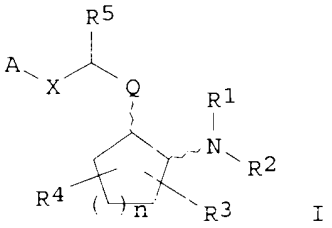

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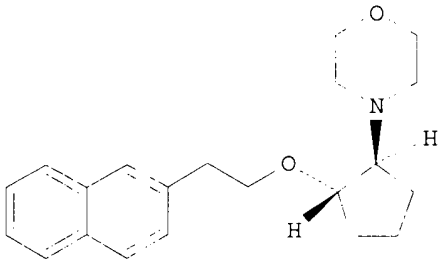

II

AB Aminocycloalkyl compds. I are disclosed [wherein n = 1, 3, 4; Q = O or OCO; X = bond, (un)substituted CH2Y, (un)substituted CH:CH; Y = bond, O, S, alkylene; R1, R2 = H, alkyl, alkoxyalkyl, hydroxyalkyl, aralkyl; or NR1R2 may form a variety of mono- or bicyclic ring systems; R3, R4 = H, OH, alkyl, alkoxy; or R3R4 may form a spiro ring with 5 or 6 members and 1 or 2 atoms of O and/or S; R5 = H, alkyl, aryl, benzyl; A = alkyl, carbocyclyl, or (un)substituted Ph, naphthyl, indenyl, indolyl, acenaphthenyl, or fluorenyl]. The compds. may be incorporated in compns. and kits. The invention also discloses a wide variety of in vitro and in vivo uses for the compds. and compns., including the treatment of arrhythmia and the prodn. of local analgesia and anesthesia. Two examples were prepd. as HCl salts, and their free bases and their salts and solvates are claimed. For instance, (1R,2R)/(1S,2S)-II.HCl (III) was prepd. by a sequence of: (1) reaction of morpholine with cyclopentene oxide; (2) mesylation of the resulting alc.; (3) etherification of the mesylate with 2-naphthaleneethanol; and (4) acidification with ethereal HCl. In a test for efficacy against cardiac arrhythmias in rats (induced by coronary artery occlusion), III had an ED50 of 1.5 .mu.M/kg/min i.v.

ST cycloalkylamine prepn antiarrhythmic sodium channel blocker; morpholinyl naphthaleneethoxy cyclopentane prepn antiarrhythmic; ketopyrrolidinyl dichlorophenethoxy cyclopentane prepn antiarrhythmic

IT Muscular dystrophy
(Becker's, treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)

IT Sexual behavior
(aphrodisiacs for; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)

IT Mental disorder
(dementia, treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)

IT Digestive tract
Respiratory tract
(disease, treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)

IT Heart, disease
(failure, treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)

IT Paralysis
(hyperkalemic periodic, treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)

IT Bladder
(incontinence, treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)

IT Intestine, disease
(irritable bowel syndrome, treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)

IT Brain, disease
Heart, disease
(ischemia, treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
IT Anesthetics
(local; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
IT Heart, disease
(long QT syndrome, treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
IT Fever and Hyperthermia
(malignant, treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
IT Muscle, disease
(paramyotonia congenita, treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
IT Allergy inhibitors
Analgesics
Anti-Alzheimer's agents
Anti-inflammatory agents
Antiarrhythmics
Antiarthritics
Antiasthmatics
Anticonvulsants
Antidepressants
Antidiabetic agents
Antihypertensives
Antihypotensives
Antimigraine agents
Antiparkinsonian agents
Antipsychotics
Antitussives
Anxiolytics
Cardiovascular agents
Immunosuppressants
Ion channel blockers
Nervous system agents
(prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
IT Ion channel blockers
(sodium; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
IT Brain, disease
(stroke, treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
IT Alopecia
Autoimmune disease
Cystic fibrosis
Eye, disease
Muscle, disease
Myasthenia gravis
Transplant rejection
(treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
IT **288394-73-0P**, (1R,2R)/(1S,2S)-2-(4-Morpholinyl)-1-(2-naphthaleneethoxy)cyclopentane monohydrochloride 288394-74-1P, (1R,2R)/(1S,2S)-2-(3-Ketopyrrolidin-1-yl)-1-(2,6-dichlorophenethoxy)cyclopentane monohydrochloride **288394-75-2P**, (1R,2R)/(1S,2S)-2-(4-Morpholinyl)-1-(2-naphthaleneethoxy)cyclopentane

288394-76-3P, (1R,2R)/(1S,2S)-2-(3-Ketopyrrolidinyl)-1-(2,6-dichlorophenethoxy)cyclopentane
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)

IT 176-33-0P, 1,4-Dioxa-7-azaspiro[4.4]nonane 95656-88-5P, N-Benzyloxycarbonyl-3-pyrrolidinol 109433-72-9P, (1R,2R)/(1S,2S)-2-(4-Morpholinyl)cyclopentanol 130312-02-6P, N-Benzyloxycarbonyl-3-pyrrolidinone 139524-57-5P, 7-Benzyloxycarbonyl-1,4-dioxa-7-azaspiro[4.4]nonane 288394-77-4P, (1R,2R)/(1S,2S)-2-(4-Morpholinyl)cyclopentyl mesylate 288394-78-5P, (1R,2R)/(1S,2S)-2-(1,4-Dioxa-7-azaspiro[4.4]non-7-yl)cyclopentanol 288394-79-6P, (1R,2R)/(1S,2S)-2-(1,4-Dioxa-7-azaspiro[4.4]non-7-yl)-1-(2,6-dichlorophenethoxy)cyclopentane
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)

IT 110-91-8, Morpholine, reactions 285-67-6, Cyclopentene oxide 501-53-1, Benzyl chloroformate 1485-07-0, 2-Naphthaleneethanol 2799-21-5 30595-79-0, 2,6-Dichlorophenethanol
RL: RCT (Reactant); RACT (Reactant or reagent)
(starting material; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)

L4 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2003 ACS
AN 1999:640819 CAPLUS
DN 131:257571
TI Preparation of aralkyl morpholinocyclohexyl ethers and analogs as antiarrhythmic agents
IN Bain, Allen I.; Beatch, Gregory N.; Longley, Cindy J.; Plouvier, Bertrand M. C.; Sheng, Tao; Walker, Michael J. A.; Wall, Richard A.; Yong, Sandro L.; Zhu, Jiqun; Zolotoy, Alexander B.
PA Nortran Pharmaceuticals Inc., Can.
SO PCT Int. Appl., 141 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C217-52
ICS C07D295-096; C07D207-04; C07D333-56; C07D207-24; C07D295-185; C07D277-04; A61K031-13; A61K031-40; A61K031-41; A61K031-535
CC 28-13 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9950225	A1	19991007	WO 1999-CA280	19990401
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2326777	AA	19991007	CA 1999-2326777	19990401

09913373

	AU 9930215	A1	19991018	AU 1999-30215	19990401
	AU 751772	B2	20020829		
	EP 1087934	A1	20010404	EP 1999-911550	19990401
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, LT, LV, FI				
	BR 9909282	A	20011016	BR 1999-9282	19990401
	EE 200000583	A	20020215	EE 2000-200000583	19990401
	JP 2002509908	T2	20020402	JP 2000-541135	19990401
	NO 2000004897	A	20001113	NO 2000-4897	20000929
PRAI	US 1998-80347P	P	19980401		
	US 1999-118954P	P	19990205		
	WO 1999-CA280	W	19990401		

OS MARPAT 131:257571

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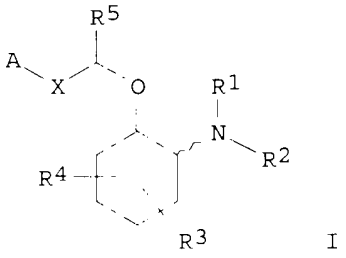


I

AB RZCHR5OZ1NR1R2 [R = (cyclo)alkyl, (un)substituted Ph, naphthyl, etc.; R1,R2 = H, (ar)alkyl, alkoxyalkyl, hydroxyalkyl; NR1R2 = heterocyclyl; R5 = H, alkyl, CH2Ph, aryl; Z = bond, (un)substituted alkylene, -CH2O, -CH:CH, etc.; Z1 = (un)substituted 1,2-cyclohexylene] were prepd. as cardiac Na channel blockers. Thus, cyclohexene oxide was aminated by morpholine and the O-mesylated product etherified by 2-naphthaleneethanol to give title compd. trans-I.

ST aralkyl morpholinocyclohexyl ether prepn antiarrhythmic agent

IT Antiarrhythmics
(morpholinocyclohexyl ethers and analogs)

IT Analgesics
(prepn. of aralkyl morpholinocyclohexyl ethers and analogs as antiarrhythmic agents)

IT Ion channel blockers
(sodium; prepn. of aralkyl morpholinocyclohexyl ethers and analogs as antiarrhythmic agents)

IT 244763-31-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BYP (Byproduct); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of aralkyl morpholinocyclohexyl ethers and analogs as antiarrhythmic agents)

IT **244762-60-5P 244762-61-6P** 244762-62-7P 244762-63-8P
244762-64-9P 244762-65-0P 244762-66-1P 244762-67-2P 244762-68-3P
244762-69-4P 244762-70-7P 244762-71-8P 244762-72-9P 244762-73-0P
244762-74-1P 244762-75-2P 244762-76-3P 244762-77-4P 244762-78-5P
244762-79-6P 244762-80-9P 244762-81-0P 244762-82-1P 244762-83-2P
244762-84-3P 244762-85-4P 244762-86-5P 244762-87-6P 244762-88-7P
244762-89-8P 244762-90-1P 244762-91-2P 244762-92-3P 244762-93-4P
244762-94-5P 244762-95-6P 244762-96-7P 244762-97-8P 244762-98-9P

244762-99-0P 244763-00-6P **244763-01-7P 244763-02-8P**
244763-03-9P 244763-04-0P 244763-05-1P 244763-06-2P 244763-07-3P
244763-08-4P 244763-09-5P 244763-10-8P 244763-11-9P 244763-12-0P
244763-13-1P 244763-14-2P 244763-15-3P 244763-16-4P 244763-17-5P
244763-18-6P 244763-19-7P 244763-20-0P 244763-21-1P 244763-22-2P
244763-23-3P 244763-24-4P 244763-25-5P 244763-26-6P 244763-27-7P
244763-28-8P 244763-29-9P 244763-30-2P 244763-32-4P 244763-33-5P
244763-34-6P 244763-35-7P 244763-36-8P 244763-37-9P 244763-38-0P
244763-39-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of aralkyl morpholinocyclohexyl ethers and analogs as antiarrhythmic agents)

IT 93-20-9, 2-(2-Naphthoxy)ethanol 110-91-8, Morpholine, reactions 111-95-5 117-34-0, Diphenylacetic acid 123-75-1, Pyrrolidine, reactions 286-20-4, Cyclohexene oxide 501-53-1, Benzyl chloroformate 504-78-9, Thiazolidine 773-99-9, 1-Naphthaleneethanol 1074-16-4, 2-Bromophenethyl alcohol 1124-63-6, 3-Cyclohexyl-1-propanol 1485-07-0, 2-Naphthaleneethanol 2799-21-5, (R)-3-Pyrrolidinol 3038-48-0, 2-Trifluoromethylphenylacetic acid 3133-87-7, Benzo[b]thiophene-3-ethanol 3929-47-3, 3-(3,4-Dimethoxyphenyl)-1-propanol 4654-39-1, 4-Bromophenethyl alcohol 5807-30-7, 3,4-Dichlorophenylacetic acid 6575-24-2, 2,6-Dichlorophenylacetic acid 7417-21-2, 3,4-Dimethoxyphenethyl alcohol 13889-98-0, 1-Acetylpiperazine 20443-98-5, 2,6-Dichlorobenzyl bromide 28229-69-8, 3-Bromobenzeneethanol 34743-88-9, 2-(4-Bromophenoxy)ethanol 227809-74-7, Benzo[b]thiophene-4-ethanol
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of aralkyl morpholinocyclohexyl ethers and analogs as antiarrhythmic agents)

IT 176-33-0P, 1,4-Dioxa-7-azaspiro[4.4]nonane 1883-32-5P 14909-79-6P 14909-81-0P 14909-84-3P 30595-79-0P 34094-21-8P 35364-79-5P 99176-18-8P 100858-33-1P 130312-02-6P 130993-58-7P 139524-57-5P 169191-80-4P 244763-40-4P 244763-41-5P 244763-42-6P 244763-43-7P 244763-44-8P 244763-45-9P 244763-46-0P 244763-47-1P 244763-48-2P 244763-49-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of aralkyl morpholinocyclohexyl ethers and analogs as antiarrhythmic agents)

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Univ British Columbia; WO 9319056 A 1993 CAPLUS
(2) Univ British Columbia; WO 9508544 A 1995 CAPLUS

L4 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2003 ACS
AN 1997:400459 CAPLUS
DN 127:108837
TI Preparation of 2-heterocyclylcyclohexyl esters as antiarrhythmics.
IN MacLeod, Bernard A.; Walker, Michael J. A.; Wall, Richard A.
PA University of British Columbia, Can.
SO U.S., 25 pp., Cont.-in-part of U.S. Ser. No. 126,575, abandoned.
CODEN: USXXAM
DT Patent
LA English
IC ICM C07D211-22
ICS C07D295-096; A61K031-445; A61K031-535
NCL 514212000

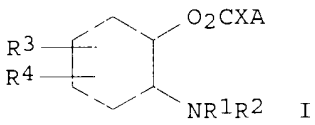
09913373

CC 27-9 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 28

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5637583	A	19970610	US 1994-313691	19940927
	CA 2172513	AA	19950330	CA 1994-2172513	19940923
	ES 2170102	T3	20020801	ES 1994-926755	19940923
	US 5885984	A	19990323	US 1997-807728	19970227
	US 6174879	B1	20010116	US 1999-271087	19990317
PRAI	US 1993-126575	B2	19930924		
	US 1994-313691	A3	19940927		
	US 1997-807728	A3	19970227		

OS MARPAT 127:108837
GI



I

AB Title compds. [I; X = bond, (CH2)nY (n = 1, 2, 3; Y = bond, O, S), CH(R12)Y (R12 = alkyl, satd. carbocyclyl, Ph, PhCH2), C(R13):CH (R13 = H, alkyl, Ph); R1, R2 = H, alkyl, alkoxyalkyl, aralkyl; R1R2N = (substituted) (ring-fused) heterocyclyl; R3, R4 = H, OH, alkyl, alkoxy, points of attachment of a spiro 5- or 6-membered heterocyclic ring contg. 1 O or S atom; A = alkyl, carbocyclyl, (substituted) Ph, naphthyl, etc.], were prepd. Thus, benzo[b]thiophene-4-acetic acid was converted to the acid chloride, which reacted with trans-2-(4-morpholinyl)cyclohexanol in CHCl3 to give trans-2-(4-morpholinyl)cyclohexyl benzo[b]thiophene-4-acetate, isolated as the hydrochloride. The latter at 8 .mu.moles/kg/min in rats gave an arrhythmia score of 0.3, vs 7 for vehicle only.

ST aminocyclohexyl ester prepn antiarrhythmic; heterocyclylcyclohexyl ester prepn antiarrhythmic

IT Antiarrhythmics
(prepn. of 2-heterocyclylcyclohexyl esters as antiarrhythmics)

IT 169191-20-2P 169191-22-4P 169191-23-5P 169191-24-6P 169191-25-7P
169191-26-8P 169191-27-9P **169191-28-0P** 169191-29-1P
169191-30-4P 169191-31-5P 169191-32-6P 169191-33-7P 169191-34-8P
169191-35-9P 169191-37-1P 169191-49-5P 169191-50-8P 169191-52-0P
169191-53-1P 169191-54-2P 169191-55-3P 169191-56-4P
169191-57-5P 169191-58-6P 169191-59-7P 169191-60-0P
169191-61-1P 169191-62-2P 169191-63-3P 169191-64-4P 169191-65-5P
169191-67-7P 169191-69-9P 169191-71-3P 169191-74-6P 169191-76-8P
169191-77-9P 192446-64-3P 192446-65-4P 192446-66-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 2-heterocyclylcyclohexyl esters as antiarrhythmics)

IT 74-88-4, Methyl iodide, reactions 86-55-5, 1-Naphthoic acid 86-87-3, 1-Naphthylacetic acid 103-82-2, Phenylacetic acid, reactions 104-03-0, 4-Nitrophenylacetic acid 109-01-3, N-Methylpiperazine 110-91-8, Morpholine, reactions 111-49-9 111-95-5 123-75-1, Pyrrolidine, reactions 283-24-9, 3-Azabicyclo[3.2.2]nonane 286-20-4, Cyclohexene oxide 286-28-2, Cyclohexene sulfide 581-96-4, 2-Naphthylacetic acid 588-22-7, 3,4-Dichlorophenoxyacetic acid 628-41-1, 1,4-Cyclohexadiene

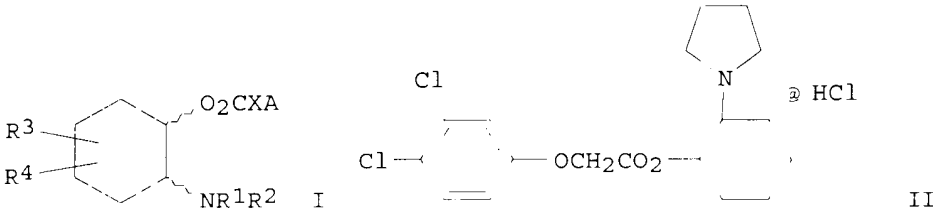
1131-09-5, Benzo[b]thiophene-3-acetic acid 1202-39-7, 3,4-Dichlorocinnamic acid 1878-68-8, 4-Bromophenylacetic acid 2635-75-8, Benzo[b]thiophene-4-acetic acid 5292-21-7, Cyclohexylacetic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of 2-heterocyclylcyclohexyl esters as antiarrhythmics)

IT 14909-79-6P 14909-81-0P 65173-64-0P 100696-05-7P 125210-15-3P 152885-54-6P 169191-78-0P 169191-79-1P 169191-80-4P 169191-81-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of 2-heterocyclylcyclohexyl esters as antiarrhythmics)

L4 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2003 ACS
AN 1995:867587 CAPLUS
DN 123:286082
TI Preparation of heterocyclohexyl esters as antiarrhythmics
IN MacLeod, Bernard A.; Walker, Michael J. A.; Wall, Richard A.
PA University of British Columbia, Can.
SO PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D295-08
ICS C07D223-14; C07D333-56; C07D333-54; C07D307-80; C07C219-24; C07C323-30; C07D307-94; A61K031-215
CC 28-17 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9508544	A1	19950330	WO 1994-CA513	19940923
	W: AU, BR, CA, CN, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, UA				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2172513	AA	19950330	CA 1994-2172513	19940923
	AU 9476502	A1	19950410	AU 1994-76502	19940923
	EP 720605	A1	19960710	EP 1994-926755	19940923
	EP 720605	B1	20011219		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	AT 211135	E	20020115	AT 1994-926755	19940923
	ES 2170102	T3	20020801	ES 1994-926755	19940923
PRAI	US 1993-126575	A	19930924		
	WO 1994-CA513	W	19940923		

OS MARPAT 123:286082
GI



AB Title compds. I (X = bond, (CH2)nY, CH(R12)Y, CR13:CH wherein n = 1-3, Y = bond, O, S, R12 = C1-6 alkyl, C3-6 carbocyclyl, Ph, PhCH2, R13 = H, C1-6

alkyl, Ph; R1, R2 =H, C3-8 alkyl, C3-8 alkoxyalkyl, C7-12 aralkyl; R1R2 = (substituted)heterocyclyl; R3, R4 = H, HO, C1-6 alkyl, C1-6 alkoxy, etc.; A = C5-12 alkyl, (substituted)Ph, etc.), a solvate or salt thereof, are prepd. I are also useful as ion e.g., Na channel blockers. Pyrrolidine, cyclohene oxide and water were reacted to give (.+-.)-trans-[2(1-pyrrolidinyl)]cyclohexanol to which was added 3,4-dichlorophenoxyacetyl chloride to give the title compd. (.+-.)-trans-II. Antiarrhythmic and Na channel blocking activity were demonstrated.

ST heterocyclyl ester prepn antiarrhythmic; ion channel blocker heterocyclyl ester prepn; pyrrolidinylcyclohexyl dichlorophenoxyacetate prepn antiarrhythmic; piperazinylcyclohexyl naphthylacetate prepn antiarrhythmic

IT Antiarrhythmics
Ion channel blockers
(prepn. of heterocyclohexyl esters as antiarrhythmics)

IT 109-01-3, 1-Methylpiperazine
RL: RCT (Reactant); RACT (Reactant or reagent)
(1prepn. of heterocyclohexyl esters as antiarrhythmics)

IT 169191-20-2P 169191-21-3P 169191-22-4P 169191-23-5P 169191-24-6P
169191-25-7P 169191-26-8P 169191-27-9P **169191-28-0P**
169191-29-1P 169191-30-4P 169191-31-5P 169191-32-6P 169191-33-7P
169191-34-8P 169191-35-9P 169191-36-0P 169191-37-1P 169191-38-2P
169191-39-3P 169191-40-6P 169191-41-7P 169191-42-8P 169191-43-9P
169191-44-0P 169191-45-1P 169191-46-2P 169191-47-3P 169191-48-4P
169191-49-5P 169191-50-8P 169191-51-9P 169191-52-0P 169191-53-1P
169191-54-2P 169191-55-3P 169191-56-4P **169191-57-5P**
169191-58-6P 169191-59-7P 169191-60-0P 169191-61-1P 169191-62-2P
169191-63-3P 169191-64-4P 169191-65-5P 169191-66-6P 169191-67-7P
169191-68-8P 169191-69-9P 169191-70-2P 169191-71-3P 169191-72-4P
169191-73-5P 169191-74-6P 169191-75-7P 169191-76-8P 169191-77-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of heterocyclohexyl esters as antiarrhythmics)

IT 86-87-3, 1-Naphthylacetic acid 103-80-0, Phenylacetyl chloride
110-89-4, Piperidine, reactions 110-91-8, Morpholine, reactions
111-49-9 111-95-5 123-75-1, Pyrrolidine, reactions 283-24-9,
3-Azabicyclo[3.2.2]nonane 286-20-4, Cyclohexene oxide 286-28-2,
Cyclohexene sulfide 586-75-4, 4-Bromobenzoyl chloride 628-41-1,
1,4-Cyclohexadiene 879-18-5, 1-Naphthoyl chloride 1871-76-7,
Diphenylacetyl chloride 2007-12-7, 1-Naphthoxyacetyl chloride
2251-65-2, 3-(Trifluoromethyl)benzoyl chloride 5078-73-9,
2-(1-Naphthyl)propionyl chloride 7031-27-8, Thiophenoxyacetyl chloride
10313-60-7, (3,4-Dimethoxyphenyl)acetyl chloride 20143-45-7,
3,4-Dichlorophenoxyacetyl chloride 20850-12-8, 3,4-Dichlorocinnamyl chloride 23860-35-7, Cyclohexylacetyl chloride 24168-51-2,
9-Fluorenecarbonyl chloride 37859-24-8, 4-Bromophenylacetyl chloride
37859-25-9, 2-Naphthylacetyl chloride 50434-36-1, 4-Nitrophenylacetyl chloride 86790-43-4, Benzofuran-2-acetyl chloride 100068-20-0,
3-Thianaphtheneacetyl chloride 129392-95-6, 1-Acenaphthenecarbonyl chloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of heterocyclohexyl esters as antiarrhythmics)

IT 3117-51-9P, 2-(1-Naphthyl)propionic acid 7581-94-4P,
trans-2-(1-Piperidinyl)cyclohexanol 14909-79-6P, trans-2-(4-Morpholinyl)cyclohexanol 14909-81-0P, trans-2-(1-Pyrrolidinyl)cyclohexanol 65173-64-0P, cis-4,5-Cyclohexenediol
100696-05-7P, trans-2-(4-Methyl-1-piperazinyl)cyclohexanol 125210-15-3P,
cis-4,5-Dimethoxycyclohexene 152885-54-6P, (1.alpha.,2.beta.,4.beta.,5.beta.)-4,5-Dimethoxy-2-(1-pyrrolidinyl)cyclohexanol 155528-15-7P,

trans-2-(Diisopropylamino)cyclohexanol 169191-78-0P,
trans-2-[N-(3-Azabicyclo[3.2.2]nonyl)]cyclohexanol 169191-79-1P,
trans-2-(1-Hexahydroazepinyl)cyclohexanol 169191-80-4P,
trans-2-[Bis(2-methoxyethyl)amino]cyclohexanol 169191-81-5P,
trans-2-(4-Morpholinyl)cyclohexanethiol 169191-82-6P,
trans-2-[Bis(2-methoxyethyl)amino]cyclohexanethiol 169191-83-7P,
7-(1-Pyrrolidinyl)-1-oxaspiro[4.5]decan-8-ol
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of heterocyclohexyl esters as antiarrhythmics)

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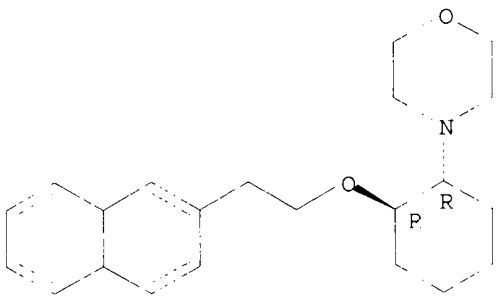
L4 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:591832 CAPLUS
DOCUMENT NUMBER: 136:63572
TITLE: pH-dependent blocking actions of three novel antiarrhythmic compounds on K+ and Na+ currents in rat ventricular myocytes
AUTHOR(S): Franciosi, S.; McLarnon, J. G.
CORPORATE SOURCE: Department of Pharmacology and Therapeutics, University of British Columbia, Faculty of Medicine, Vancouver, BC, V6T 1Z3, Can.
SOURCE: European Journal of Pharmacology (2001), 425(2), 95-107
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Three novel chem. related compds. were studied for their pH-dependent ion channel blocking actions on the transient outward K+ current (Ito) and the Na+ current (INa) in isolated rat ventricular myocytes. The (.+-.)-trans-naphthylethoxycyclohexylamines, RSD1108, RSD1070 and RSD1067, showed similar potencies in reducing the inactivation time course of Ito at pH 7.4. However, RSD1108 (pKa 6.8) was a more potent blocker of Ito at pH 6.4 than the other two compds. (pKa values near 8.0). The redn. of inactivation times induced by the RSD compds. was consistent with open channel blockade and in consequence an open channel block model was used in order to est. blocking and unblocking rate consts. This anal. showed no apparent correlation between pKa and onward blocking rate consts. for the compds. However, the unblocking rate const. for the low pKa compd. RSD1108 at acid pH decreased markedly from that found at normal pH. Both RSD1108 and RSD1070 showed an enhanced potency to block INa at acid pH relative to pH 7.4. However, RSD1108 showed significantly less inhibition of INa at both pH values compared to RSD1070 and RSD1067. Differences in channel block were also evident between RSD1070 and RSD1067, which could be attributed to the difference in naphthyl groups between their chem. structures. The compds. exhibited use- and frequency-dependent blockade of INa with the amt. of use-dependent blockade greater for RSD1108 and RSD1067 than for RSD1070 at acid pH compared to neutral pH. Greater frequency-dependent inhibition was apparent for RSD1108 as compared to RSD1070 and RSD1067 at both pH 7.4 and 6.4. These results point out the importance of the magnitude of pKa and chem. structure in ion channel blocking actions of a series of structurally related compds.
IT **244762-60-5**, RSD 1067
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)
(pH-dependent blocking actions of novel antiarrhythmic compds. on K+

and Na+ currents in rat ventricular myocytes)
RN 244762-60-5 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyl)ethoxy]cyclohexyl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



● HCl

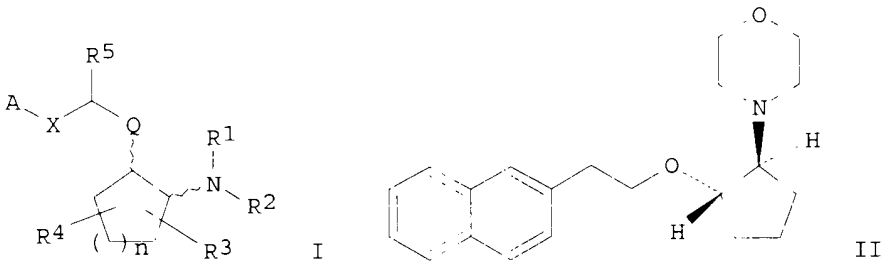
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:573767 CAPLUS
DOCUMENT NUMBER: 133:176973
TITLE: Cycloalkyl amine compounds and their use as antiarrhythmics and sodium channel blockers
INVENTOR(S): Beatch, Gregory N.; Plouvier, Bertrand M. C.; Walker, Michael J. A.; Wall, Richard A.; Zolotoy, Alexander B.
PATENT ASSIGNEE(S): Nortran Pharmaceuticals Inc., Can.
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000047547	A2	20000817	WO 2000-CA117	20000210
WO 2000047547	A3	20001214		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-119887P P 19990212
OTHER SOURCE(S): MARPAT 133:176973
GI



I II

AB Aminocycloalkyl compds. I are disclosed [wherein n = 1, 3, 4; Q = O or OCO; X = bond, (un)substituted CH2Y, (un)substituted CH:CH; Y = bond, O, S, alkylene; R1, R2 = H, alkyl, alkoxyalkyl, hydroxyalkyl, aralkyl; or NR1R2 may form a variety of mono- or bicyclic ring systems; R3, R4 = H, OH, alkyl, alkoxy; or R3R4 may form a spiro ring with 5 or 6 members and 1 or 2 atoms of O and/or S; R5 = H, alkyl, aryl, benzyl; A = alkyl, carbocyclyl, or (un)substituted Ph, naphthyl, indenyl, indolyl, acenaphthenyl, or fluorenyl]. The compds. may be incorporated in compns. and kits. The invention also discloses a wide variety of in vitro and in vivo uses for the compds. and compns., including the treatment of arrhythmia and the prodn. of local analgesia and anesthesia. Two examples were prepd. as HCl salts, and their free bases and their salts and solvates are claimed. For instance, (1R,2R)/(1S,2S)-II.HCl (III) was prepd. by a sequence of: (1) reaction of morpholine with cyclopentene oxide; (2) mesylation of the resulting alc.; (3) etherification of the mesylate with 2-naphthaleneethanol; and (4) acidification with ethereal HCl. In a test for efficacy against cardiac arrhythmias in rats (induced by coronary artery occlusion), III had an ED50 of 1.5 .mu.M/kg/min i.v.

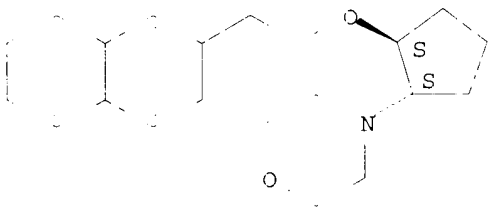
IT **288394-73-0P**, (1R,2R)/(1S,2S)-2-(4-Morpholinyl)-1-(2-naphthaleneethoxy)cyclopentane monohydrochloride **288394-75-2P**, (1R,2R)/(1S,2S)-2-(4-Morpholinyl)-1-(2-naphthaleneethoxy)cyclopentane
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)

RN 288394-73-0 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyl)ethoxy]cyclopentyl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

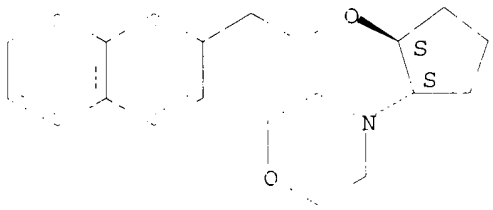
09913373



● HCl

RN 288394-75-2 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyl)ethoxy]cyclopentyl]-, rel-
(9CI) (CA INDEX NAME)

Relative stereochemistry.



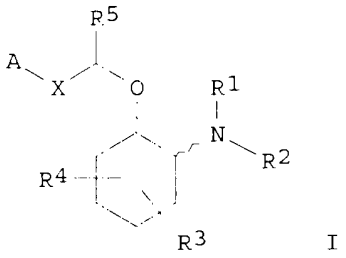
L4 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:640819 CAPLUS
DOCUMENT NUMBER: 131:257571
TITLE: Preparation of aralkyl morpholinocyclohexyl ethers and analogs as antiarrhythmic agents
INVENTOR(S): Bain, Allen I.; Beatch, Gregory N.; Longley, Cindy J.; Plouvier, Bertrand M. C.; Sheng, Tao; Walker, Michael J. A.; Wall, Richard A.; Yong, Sandro L.; Zhu, Jiqun; Zolotoy, Alexander B.
PATENT ASSIGNEE(S): Nortran Pharmaceuticals Inc., Can.
SOURCE: PCT Int. Appl., 141 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9950225	A1	19991007	WO 1999-CA280	19990401

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,

	CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2326777		AA	19991007	CA 1999-2326777	19990401
AU 9930215		A1	19991018	AU 1999-30215	19990401
AU 751772		B2	20020829		
EP 1087934		A1	20010404	EP 1999-911550	19990401
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, LT, LV, FI				
BR 9909282		A	20011016	BR 1999-9282	19990401
EE 200000583		A	20020215	EE 2000-200000583	19990401
JP 2002509908		T2	20020402	JP 2000-541135	19990401
NO 2000004897		A	20001113	NO 2000-4897	20000929
PRIORITY APPLN. INFO.:				US 1998-80347P P	19980401
				US 1999-118954P P	19990205
				WO 1999-CA280 W	19990401

OTHER SOURCE(S): MARPAT 131:257571
GI



I

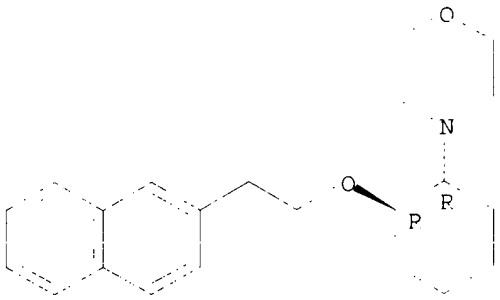
AB RZCHR5OZ1NR1R2 [R = (cyclo)alkyl, (un)substituted Ph, -naphthyl, etc.; R1,R2 = H, (ar)alkyl, alkoxyalkyl, hydroxyalkyl; NR1R2 = heterocyclyl; R5 = H, alkyl, CH2Ph, aryl; Z = bond, (un)substituted alkylene, -CH2O, -CH:CH, etc.; Z1 = (un)substituted 1,2-cyclohexylene] were prepd. as cardiac Na channel blockers. Thus, cyclohexene oxide was aminated by morpholine and the O-mesylated product etherified by 2-naphthaleneethanol to give title compd. trans-I.

IT **244762-60-5P 244762-61-6P 244763-01-7P 244763-02-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of aralkyl morpholinocyclohexyl ethers and analogs as antiarrhythmic agents)

RN 244762-60-5 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyl)ethoxy]cyclohexyl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

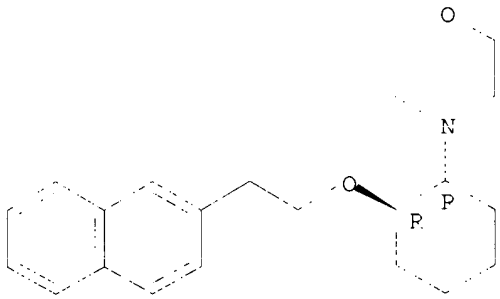
Relative stereochemistry.



● HCl

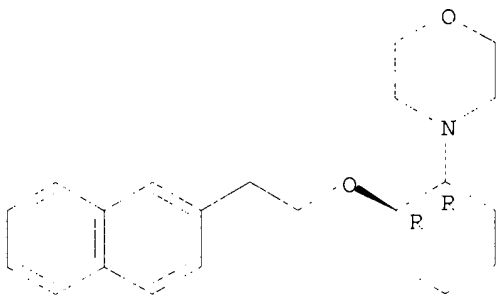
RN 244762-61-6 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyl)ethoxy]cyclohexyl]-, rel-
(9CI) (CA INDEX NAME)

Relative stereochemistry.



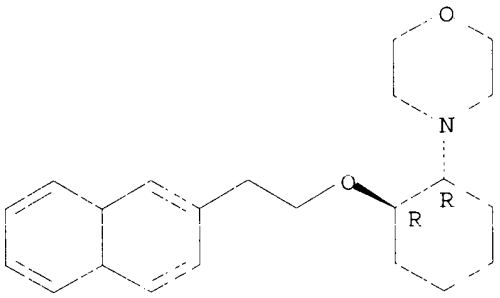
RN 244763-01-7 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyl)ethoxy]cyclohexyl]-, rel-(+)-
(9CI) (CA INDEX NAME)

Rotation (+). Absolute stereochemistry unknown.



RN 244763-02-8 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyl)ethoxy]cyclohexyl]-, rel-(-)-
(9CI) (CA INDEX NAME)

Rotation (-). Absolute stereochemistry unknown.

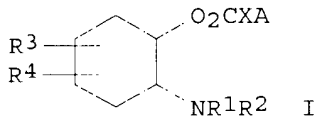


REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:400459 CAPLUS
DOCUMENT NUMBER: 127:108837
TITLE: Preparation of 2-heterocyclylcyclohexyl esters as antiarrhythmics.
INVENTOR(S): MacLeod, Bernard A.; Walker, Michael J. A.; Wall, Richard A.
PATENT ASSIGNEE(S): University of British Columbia, Can.
SOURCE: U.S., 25 pp., Cont.-in-part of U.S. Ser. No. 126,575, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5637583	A	19970610	US 1994-313691	19940927
CA 2172513	AA	19950330	CA 1994-2172513	19940923
ES 2170102	T3	20020801	ES 1994-926755	19940923
US 5885984	A	19990323	US 1997-807728	19970227
US 6174879	B1	20010116	US 1999-271087	19990317

PRIORITY APPLN. INFO.: US 1993-126575 B2 19930924
US 1994-313691 A3 19940927
US 1997-807728 A3 19970227
OTHER SOURCE(S): MARPAT 127:108837
GI



I

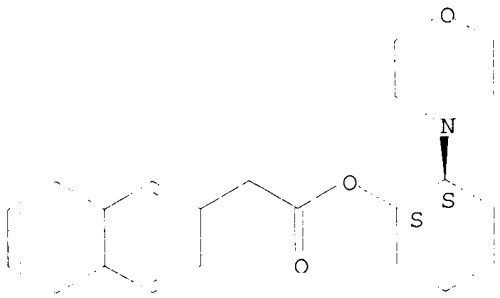
AB Title compds. [I; X = bond, (CH2)nY (n = 1, 2, 3; Y = bond, O, S), CH(R12)Y (R12 = alkyl, satd. carbocyclyl, Ph, PhCH2), C(R13):CH (R13 = H, alkyl, Ph); R1, R2 = H, alkyl, alkoxyalkyl, aralkyl; R1R2N = (substituted) (ring-fused) heterocyclyl; R3, R4 = H, OH, alkyl, alkoxy, points of

attachment of a spiro 5- or 6-membered heterocyclic ring contg. 1 O or S atom; A = alkyl, carbocyclyl, (substituted) Ph, naphthyl, etc.], were prepd. Thus, benzo[b]thiophene-4-acetic acid was converted to the acid chloride, which reacted with trans-2-(4-morpholinyl)cyclohexanol in CHCl3 to give trans-2-(4-morpholinyl)cyclohexyl benzo[b]thiophene-4-acetate, isolated as the hydrochloride. The latter at 8 .mu.moles/kg/min in rats gave an arrhythmia score of 0.3, vs 7 for vehicle only.

IT **169191-28-0P 169191-57-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 2-heterocyclylcyclohexyl esters as antiarrhythmics)

RN 169191-28-0 CAPLUS
CN 2-Naphthaleneacetic acid, 2-(4-morpholinyl)cyclohexyl ester, hydrochloride, trans- (9CI) (CA INDEX NAME)

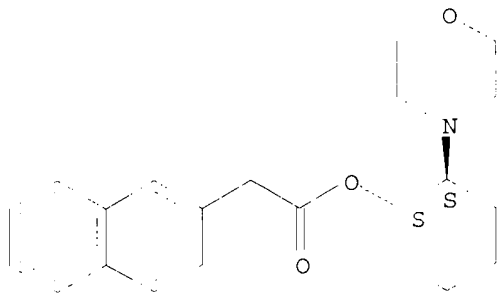
Relative stereochemistry.



● HCl

RN 169191-57-5 CAPLUS
CN 2-Naphthaleneacetic acid, 2-(4-morpholinyl)cyclohexyl ester, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L4 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:867587 CAPLUS
DOCUMENT NUMBER: 123:286082
TITLE: Preparation of heterocyclohexyl esters as

09913373

antiarrhythmics

INVENTOR(S): MacLeod, Bernard A.; Walker, Michael J. A.; Wall, Richard A.

PATENT ASSIGNEE(S): University of British Columbia, Can.

SOURCE: PCT Int. Appl., 91 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

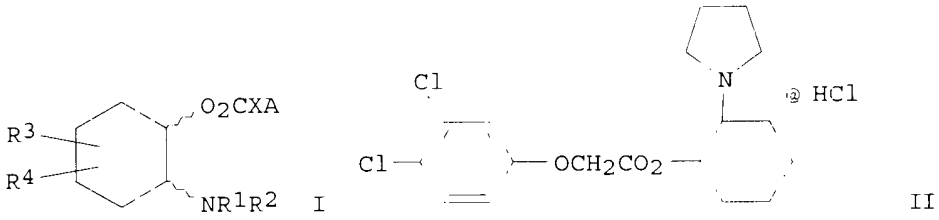
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9508544	A1	19950330	WO 1994-CA513	19940923
W: AU, BR, CA, CN, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, UA				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2172513	AA	19950330	CA 1994-2172513	19940923
AU 9476502	A1	19950410	AU 1994-76502	19940923
EP 720605	A1	19960710	EP 1994-926755	19940923
EP 720605	B1	20011219		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
AT 211135	E	20020115	AT 1994-926755	19940923
ES 2170102	T3	20020801	ES 1994-926755	19940923

PRIORITY APPLN. INFO.: US 1993-126575 A 19930924
WO 1994-CA513 W 19940923

OTHER SOURCE(S): MARPAT 123:286082

GI



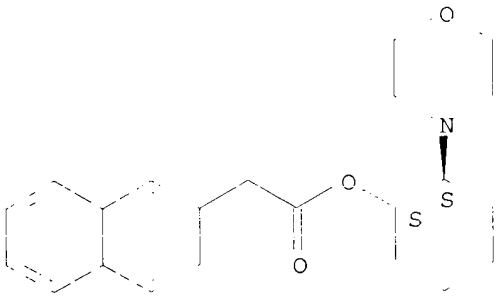
AB Title compds. I (X = bond, (CH2)nY, CH(R12)Y, CR13:CH wherein n = 1-3, Y = bond, O, S, R12 = C1-6 alkyl, C3-6 carbocyclyl, Ph, PhCH2, R13 = H, C1-6 alkyl, Ph; R1, R2 =H, C3-8 alkyl, C3-8 alkoxyalkyl, C7-12 aralkyl; R1R2 = (substituted)heterocyclyl; R3, R4 = H, HO, C1-6 alkyl, C1-6 alkoxy, etc.; A = C5-12 alkyl, (substituted)Ph, etc.), a solvate or salt thereof, are prepd. I are also useful as ion e.g., Na channel blockers. Pyrrolidine, cyclohene oxide and water were reacted to give (.+-.)-trans-[2(1-pyrrolidinyl)]cyclohexanol to which was added 3,4-dichlorophenoxyacetyl chloride to give the title compd. (.+-.)-trans-II. Antiarrhythmic and Na channel blocking activity were demonstrated.

IT **169191-28-0P 169191-57-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of heterocyclohexyl esters as antiarrhythmics)

RN 169191-28-0 CAPLUS

CN 2-Naphthaleneacetic acid, 2-(4-morpholinyl)cyclohexyl ester, hydrochloride, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



● HCl

PN 169191 57-5 CAPLUS
CN 2-Naphthaleneacetic acid, 2-(4-morpholinyl)cyclohexyl ester, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.